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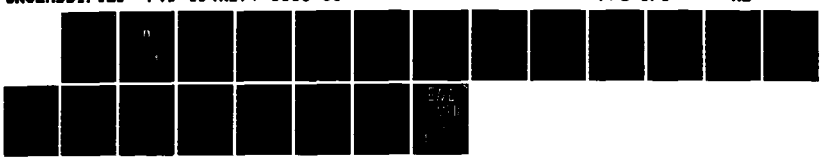

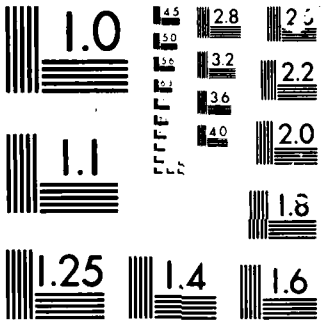

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FOREIGN TECHNOLOGY DIVISION

AN ANIMAL EXPERIMENT OF THE FLUORESCENCE EFFECTS AND THE SIDE-EFFECTS OF THE LIGHT SENSITIVE TECHNIQUES

by

Jiang Xin, Qi Jingfang, et al.

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HUMAN TRANSLATION

FTD-ID(RS)T-0005-86 10 April 1986

MICROFICHE NR: FTD-86-C-001712

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English pages: 16

Source: Zhong Quo Jiguang, Vol. 11, Nr. 9, 1984, pp. 567-571

Country of origin: China
Translated by: SCITRAN
F33657-84-D-0165
Requester: FTD/SDEO

PREPARED BY

TRANSLATION DIVISION
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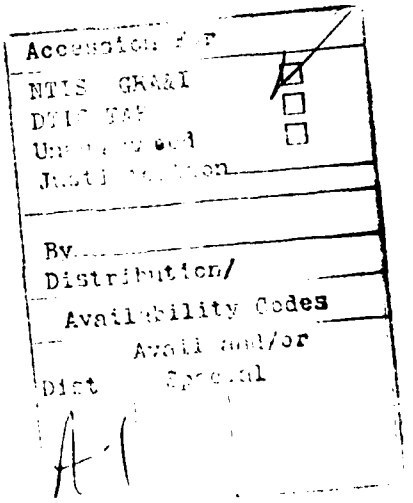

An Animal Experiment of the Fluorescence Effects and the Side-Effects of the Light Sensitive Techniques

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ABSTRACT

The animal experiments suggest that small white mice with sarcoma and liver cancer, in which HPD and fluorescein sodium are injected into the abdominal cavities, have intenser fluorescence in tumours than in normal tissue when they are irradiated by an He-Cd laser. and various types of lights have different effects on the small white mice injected with HPD: sunlight has the greatest effect, and a 100 W electric light has the next: and HPD has some side-effects on the liver of small white mice.

Using light sensitive techniques to diagnose and cure cancer is a new topic under active study all over the world. The dyes used as the sensitizers are HPD, fluorescein sodium.

etc. HPD is the most widely used, and fluorescein sodium is the second widely used. In order to compare their fluorescence effects and effects of different light sources to the HPD in the process of application, we have conducted a series of animal experiments. The results of our experiments are reported in this paper.

1. The Animal Experiments

A total of 336 small white mice were used in the experiments. Among them, 32 were transplanted with S_{180} sarcoma, 32 were transplanted with ascites type liver cancer, and the other 272 were the normal ones with weight about 18~22 grams.

2. Experimental Sensitizers

(1) HPD. A powder, produced by Yangzhou Biological Products Factory , was diluted into a brown-red solution with 5 % glucose sodium-chloride solution when it was used. This dose was injected into the tail veins or abdominal cavities of the small white mice with the appropriate body-weight doses.

(2) Fluorescein sodium. It was manufactured as a powder by Shanghai's Second Factory of Testing Chemicals. 25 grams per bottle. When it was used, a 5 % concentration yellow-

green solution was prepared and was injected into the abdominal cavities or tail veins of the small white mice.

3. Experimental Light Sources

Sun light, a 100 watt incandescent lamp, a 60 watt incandescent lamp, natural light, dark room, He-Cd laser were used as light sources. The He-Cd laser was made by Jiangsu Laser Research Institute and has a power output of 30 milli-watts, a light spot of 3 mm in diameter, and a wavelength of 4416 A.

4. Experimental Method and Results

(1) The fluorescent effects

24 mice with S_{180} sarcoma and another 24 mice with ascites type liver cancer were chosen for observation, and each section was divided into two groups with 12 mice. Each group was divided into three sub-groups and each sub-group consisted of four mice. HPD and flourescein sodium were injected into their abdominal cavities with the doses equivalent to one, two, and four times of the human normal dose. The He-Cd laser was used to irradiate these mice at different times after the injection. Then we observed the fluorescence of the sarcoma, ascites position, and the normal tissues, compared with the four mice which also

carried sarcoma and ascites type liver cancer but had not been injected HPD and fluorescein sodium. The results are listed in table 1 and 2.

The above sub-groups 1, 2, 3 of mice carrying S_{180} sarcoma and ascites type liver cancer had no fluorescence before the He-Cd irradiation, and therefore all had negative reactions.

From tables 1. and 2. we can see that: a) after a 6 hour irradiation with the He-Cd laser, the mice carrying S_{180} sarcoma and ascites type liver cancer and injected with 5~20 mg/kg HPD can produce orange color fluorescence in both tumour and normal tissues. Such fluorescence was most intense within 24-48 hours, and the boundary between the tumour and normal tissues was most clear. After 48 hours, the fluorescence became weak gradually and disappeared in the position of non-cancer tissues. Those only injected with HPD but without He-Cd laser irradiation, or only irradiated with He-Cd laser but without HPD injection did not produce fluorescence.

(b) The above two types of the white mice, irradiated with the He-Cd laser one hour after the injection with 20~80 mg/kg fluorescein sodium, produced obvious yellow-green fluorescence in the tumour tissues but the fluorescence in the normal tissues was quite weak. After 24 hours the fluorescence in the tumour position became obviously weak

and the fluorescence in the normal tissues disappeared gradually. After 48 hours, the fluorescence disappeared totally. Those only injected with fluorescien sodium but without He-Cd laser irradiation, or only irradiated with He-Cd laser but without fluorescein sodium did not produce fluorescence.

(2) The influence of different light sources to the small white mice injected with HPD

(a) Sun light group

We took 104 normal mice and divided them into two groups. Each group had 54 mice and they were divided into four sub-groups. One group was injected into the abdominal cavities with HPD 2~3 times of the normal dose. The other group was injected into the tail veins with HPD. Each sub-group was placed under sun light for different times after the injection. Then they were compared with the four normal mice without the injection of HPD, respectively. The results are listed in table 3.

(b) Incandescent lamp light, natural light, and dark room

We took 88 normal white mice and divided them into four groups. The first group had 24 mice, and the others had 16. Each group was divided into two sub-groups and were injected into the abdominal cavities and the tail veins with a normal and three times of the normal doses separately. After the

injection, two groups were placed under the light of a 100-watt and a 60-watt incandescent lamp respectively. The distance between them was about 90 cm, and they were irradiated for a countinuous period of 10 days (8 hours each day). The other two groups were under the natural light and in the dark room for half a month, and were compared with the four normal white mice without PHD injection. As a result, on the 7th day, in the group under the 100-watt lamp, three mice with a three-time dose injection of HPD had swollen faces, preferred to sleep, and died on the 8~9th day. The pathology diagnosis was that the liver cells had acid addictive change and dispersive inflammation, the lungs were slightly blood filled, but the hearts, kidneys and skin were normal. The activity of the other 21 mice began to slow and their diet was decreased at the beginning of the light irradiation. They became normal after 2~4 days and no one died. After half a month two of them were selected arbitrarily and killed for pathology diagnosis. Their liver cells had dispersive inflammation, the lungs of a few of them had lymphocyte infiltration, and the hearts and kidneys were normal. The other three groups - the 60-watt lamp group, the natural light group, and the dark room group, were similar to the comparative group and no one died. After half a month two mice were arbitrarily selected from each groupand were killedfor pathology diagnosis. Their

liver cells had dispersive inflammation, but the hearts, lungs, kidneys, and skin were all normal. The comparative group had no abnormal changes.

5. DISCUSSION

(1) Fluorescein sodium can produce different intensity fluorescence in both tumours and normal tissue one hour after the injection, but HPD requires 24-48 hours to produce fluorescence. Considering that the side-effects of fluorescein sodium are far less than those of HPD, and combining our experience of diagnosing 210 patients for ear, nose, and throat cancers with fluorescein sodium taken orally, we think that in the application of the light sensitive techniques to the diagnosis of cancers on the body surface and open cavities and channels, fluorescein sodium is a better choice. This is especially important in the large scale preventative investigation.

(2) According to the result of the first and second groups which were under sun light, the injection with 2-3 times of the normal doses of HPD and placing under sun light within 48 hours lead to the death of the small white mice. The speed of death was correlated to the dose. The mice with three times the normal dose died faster than those with the normal dose. According to the disease symptom and the pathology diagnosis, the cause of the death of the small

white mice might be related to allergy.

(3) According to the experiments of the third and fourth sub-groups in the sun light groups, the eight small white mice with abdominal cavity injections of HPD all died after sun light irradiation, but the tail-vein-injected small white mice, although they had abnormal effects after the irradiation, recovered quickly. This manifests that the absorption and excretion rate of the abdominal injection is slower and HPD stays in the mice body longer. This leads to the fact that the mice with abdominal injections still had higher body concentrations of HPD on the fifth day and therefore were more sensitive to the sun light thus causing the death of the small white mice. But for the tail-vein-injected small white mice, because the absorption and excretion rate was faster, the body concentration of HPD on the fifth day was lower. Thus although they had some abnormal effects, the effects were light and they recovered after a few days.

(4) According to the results of mice injected with HPD and placed under the 100-watt incandescent lamp, the small white mice injected with HPD were not sensitive to the 100-watt lamp and the influence was not large. Among them three had allergic reactions on the seventh day and then died gradually. This was possibly caused by the individual differences of the mice. It manifests that the allergic

reactions of the HPD injected mice might be some kind of slow reaction. According to the conclusions 2 and 4, in the application of HPD in clinics, patients should avoid sun light and 100-watt lamps to prevent negative effects.

(5) For all the groups injected with HPD, the liver cells had slight changes and inflammation. But for most of the comparative mice without HPD injection, the liver changes were not obvious. This shows that HPD has some side-effects to liver and this suggests that, before the application of HPD, liver diagnosis should be made for patients. If the liver of a patient has abnormal changes, HPD should be applied very carefully.

Table 1. HPD + He-Cd laser effects to S_{180} carsoma and ascites type liver cancer of small white mice (the first group)

表1 HPD+He-Cd 激光对 S_{180} 肉瘤和腹水型肝癌小白鼠的荧光效应(第一大组) 1

分组 2			第1组 3								第2组 4								第3组 5								对照组 6	
HPD剂量 7			常量 8 (5毫克/千克) 12								二倍量 9 (10毫克/千克) 13								四倍量 10 (20毫克/千克) 14								未注射 11 HPD	
注射HPD至激光照射间隔时间(小时) 15 16			6		24		48		72		6		24		48		72		6		24		48		72		6, 24, 48, 72	
			A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B		
荧光效应 17	1	C	++	+	+	±	+	−	−	−	+	±	+	±	+	−	±	−	+	+	+	±	++	−	+	−	A B	
		D	+	+	+	+	−	±	+	−	+	±	++	+	++	+	+	±	++	++	++	++	++	+	+	−		
	2	C	+	±	+	±	+	−	±	−	++	+	++	±	+	−	±	−	+	±	++	+	++	+	±	−	均为阳性 18	
		D	+	+	+	+	+	±	−		+	+	++	±	++	+	+	±	++	+	++	+	++	±	+	−		
	3	C	+	±	++	+	+	±	±	−	+	+	++	−	+	−	±	−	++	+	++	±	++	±	+	−	(−)	
		D	+	+	+	+	±	+	−	−	+	±	+	±	+	−	+	−	++	+	++	+	++	+	+	±		
	4	C	++	++	++	+	+	−	±	−	++	++	++	−	++	±	+	−	+	+	+	−	±	−	−	−		
		D	−	±	+	±	±	−	±	−	++	+	++	+	++	+	+	−	+	+	++	+	++	+	+	−		

19 A代表肉瘤部位荧光，B代表正常组织荧光，C代表腹水型肝癌小白鼠，D代表 S_{180} 肉瘤小白鼠。

20 注：++——表示荧光为强阳性，即用肉眼能明显辨别 HPD 的桔红色荧光与荧光素钠的黄绿色荧光。+——表示荧光弱阳性，即用肉眼可看出较弱的桔红色或黄绿色荧光。±——表示有可疑荧光，即用肉眼仔细辨认可看出很弱的桔红色或黄绿色荧光。−——表示无荧光，即用肉眼不能看出桔红色或黄绿色荧光。(下同)

1-caption; 2-sub-group; 3-the first sub-group; 4-the second sub-group; 5-the third sub-group; 6-the comparative group; 7-HPD dose; 8-normal dose; 9-twice of normal dose; 10-four times of normal dose; 11-uninjected; 12-mg/kg; 13-mg/kg; 14-mg/kg; 15- Time between HPD injection and laser irradiation; 16-hour; 17-flourescence effect; 18-all reactions are negative; 19- "A" denotes fluorescence in cancer tissue, "B" denotes fluorescence in normal tissues, "C" denotes ascites type cancer, and "D" denotes S_{180} sarcoma 20-notes: "++" denotes fluorescence is strong positive, that is: the orange HPD fluorescence and the yellow-green fluorescence of fluorescein sodium can be observed easily by human eyes. "+" denotes the fluorescence is weak positive and the weak orange and yellow-green fluorescence can still be observed by human eyes. "$\pm$" denotes the suspectable fluorescence, that is: the very weak orange and yellow-green fluorescence still can be seen by careful observation. "-" denotes no fluorescence, that is: no fluorescence can be observed by human eyes. (The notations are the same in table 2.)

Table 2. Fluorescein sodium + He-Cd effects to carsoma and ascites type liver cancer of small white mice (the second group)

表2 荧光素钠 +He-Cd 激光对 S_{180} 肉瘤与腹水型肝癌小白鼠的荧光效应(第二大组)

分组			第1组								第2组								第3组								对照组	
荧光素钠剂量			常量 (20毫克/千克)								二倍量 (40毫克/千克)								四倍量 (80毫克/千克)								未注射荧光素钠	
注射荧光素钠至激光照射间隔时间(小时)			1		24		48		72		1		24		48		72		1		24		48		72		1, 24, 48, 72	
			A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B
荧光效应	1	C	++	+	+	±	±	-	-	-	++	+	+	±	±	-	-	-	++	++	++	±	±	-	-	-		
		D	++	+	+	-	-	-	-	-	++	+	+	-	-	-	-	-	++	+	+	±	-	-	-	-		
	2	C	++	+	+	-	±	-	-	-	++	+	+	-	±	-	-	-	++	+	+	±	±	-	-	-		
		D	++	+	+	-	-	-	-	-	++	+	+	-	-	-	-	-	++	+	+	-	-	-	-	-		
	3	C	++	++	+	±	-	-	-	-	++	+	+	-	-	-	-	-	++	+	+	-	±	-	-	-		
		D	++	++	±	-	-	-	-	-	++	±	+	-	-	-	-	-	++	+	+	-	-	-	-	-		
	4	C	++	+	+	-	-	-	-	-	++	+	+	±	-	-	-	-	++	+	+	±	±	-	-	-		
		D	++	+	+	±	-	-	-	-	++	-	+	±	-	-	-	-	++	++	+	±	-	-	-	-		

均为阴性 (-)

1-caption; 2-sub-group; 3-the first group; 4-the second group; 5-the third group; 6-comparative group; 7-fluorescein sodium dose; 8-normal dose; 9-twice of normal dose; 10-four times of normal dose; 11-uninjected; 12-mg/kg; 13-mg/kg; 14-mg/kg; 15-time between dose injection and laser irradiation; 16-effect of fluorescence; 17-all are negative.

Table 3. The influence of sun light to the small white mice injected with HPD

表3 太阳光对注入 HPD 正常小白鼠的影响

分组	第1组								第2组					
HPD 剂量	常量		二倍量		三倍量		对照组		常量		三倍量		对照量	
小白鼠数目(只)	A	B	A	B	A	B	A	B	A	B	A	B	A	B
	4	4	4	4	4	4	4	4	4	4	4	4	4	4
注射后至太阳光照射间隔时间(小时)	半		半		半				48		48			
太阳光照射时间(小时)	2		2		3		2		3		3		3	
照射结果	照射过程中全部先兴奋乱跳乱咬，约数分钟后呼吸加快抽搐死亡						正常		4只A组与3只B组于照射后一二天全部死亡，另一只B组第7天死亡		3只A组与4只B组于照射中或照射后全部死亡。1只A组于照射后次日死亡		正常	
病理检查	肝：门静脉及中央静脉较明显扩张充血，肝窦或汇管区内有少量淋巴细胞浸润 肺：支气管有程度不等淋巴细胞浸润，心肌、肾、皮肤正常						A组中3只正常，1只肝内有散在性炎症，B组均正常		肝：门静脉均轻度充血，肝细胞有增酸性变与散在性炎症 肺：支气管有淋巴细胞浸润，心肾皮肤正常				A组全部正常，B组中3只正常，1只肺内有散在性炎症	

分组	第3组						第4组					
HPD 剂量	常量		三倍量		对照量		常量		三倍量		对照组	
小白鼠数目(只)	A	B	A	B	A	B	A	B	A	B	A	B
	4	4	4	4	4	4	4	4	4	4	4	4
注射后至太阳光照射时间间隔(小时)	120		120				11天		11天			
太阳光照射时间(小时)	3		3		3		3		3		3	
照射结果	A组于照射后第二、三天内全部死亡		A组于照射后二小时内全部死亡		正常		正常		A组于照射当日饮食活动稍减，次日恢复正常，B组均正常		正常	
	8只B组于照射后出现面肿，嗜睡，眼脸缩小，3~4天好转，5~6天恢复。											
病理检查	8只A组肝肺肾轻度充血变性，心皮肤正常。 8只B组肝细胞有增酸性变，心肺肾皮肤正常				正常		肝或肺内有散在性炎症，皮肤、心肾正常				A组均正常，B组中3只正常，1只肺内有散在性炎症	

注：(1) A代表从腹腔内注入HPD的小白鼠，B代表从尾静脉注入HPD的小白鼠

(2) 太阳光对注入黄光素钠的80只小白鼠影响。经同法实验与对照组相似。

1-caption; 2-sub-group; 3-the first group; 4-the second group; 5-HPD dose; 6-normal; 7-twice of normal dose; 8-four times of normal dose; 9-comparative group; 10-normal dose; 11-twice of normal dose; 12-comparative group; 13-number of small white mice; 14-time between dose injection and sun light irradiation; 15-time of sun light irradiation (hours); 16-result of irradiation; 17-0.5; 18-0.5; 19-0.5; 20-during the irradiation all are activized at first and then after a few minutes the breath was accelerated and then died; 21-normal; 22-four of sub-group A and three of sub-group B died after 1-2 days of the irradiation; another one of sub-group B died on the seventh day; 23-three of the sub-group A and four of the sub-group B died during or after the irradiation; the another one of the sub-group A died on the second day after the irradiation; 24-normal; 25-pathology diagnosis; 26-liver: the gate vein and the central vein had obvious expansion and filled with blood, liver and collection tubes had slight lymphocyte infiltration, lungs had different degree of lymphocyte infiltration in the bronchuses, heart muscle, kidneys, and skin were normal; 27-three of group A were normal, the other one had dispersive inflammation in liver, all of group B were normal; 28-liver: gate veins were all slightly blood filled, liver cells were acid addictive and had dispersive inflammation, lung: lymphocyte infiltration in bronchuses, but hearts, kidneys,

and skin were normal; 29-all of Group A were normal; three of group B were normal, the other one had dispersive inflammation effect in the lung; 30-sub-group; 31-the third group; 32-the fourth group; 33-HPD dose; 34-normal; 35-three times of normal dose; 36-comparative group; 37-normal; 38-three times of normal dose; 39-comparative group; 40-number of small white mice; 41-time between dose injection and sun light irradiation; 42-days; 43-days; 44-time of sun light irradiation; 45-result of irradiation; 46-all of group A died on the second or third day after light irradiation; 47-all of group A died after two hours of irradiation; 48-normal; 49-normal; 50-group A had decreased diet in the first day of irradiation, and recovered on the second day, group B were normal; 51-normal; 52-eight of group B had swollen faces effect, sleep preference, and diminished eye lids, the effects became less after 3-4 days, and they recovered after 5-6 days. 53-pathology diagnosis; 54-eight of group A had blood-filled changes in livers, lungs, and kidneys, but hearts and skin were normal, eight of group B had scid addictive effect of liver cells, but hearts, lungs, kidneys and skin were normal; 55-normal; 56-dispersive inflammation effects in livers and lungs, but skin, hearts, and kidneys were normal; 57-group A were normal, three of group B were normal, the other one had dispersive inflammation effect; 58-notes: (1) "A" denotes

the small white mice with HPD injected into the abdominal cavities, "B" denotes the small white mice with HPD injected into tail veins. (2) The effect of sun light on the 80 small white mice injected with fluorescein sodium were similar to the comparative group.

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